

REPLY

Serial No. 09/523,237
Atty. Docket No. GP068-03.CN1

The Examiner first alleges that the invention of claims 442-457 and the invention of claims 458-467, 472-484 and 489-491 are related as combination and subcombination. Specifically, the Examiner contends that the combination as claimed does not require the particulars of the subcombination as claimed *because the additional limitation of including a promoter sequence in the combination could confer patentability* so that the subcombination as claimed is not required for patentability. Applicants submit that the Examiner has misconstrued what constitutes a combination or subcombination in this case. In claim 458, for example, the claimed kit comprises *inter alia* an unlabeled amplification oligonucleotide. In the section of the specification entitled "Modified Nucleic Acid Amplification Oligonucleotides," amplification oligonucleotides are described as including "oligonucleotide primers, promoter-primers, and/or splice templates for nucleic acid amplification and compositions comprising such oligonucleotides." See specification at paragraph bridging pages 22 and 23. Thus, while the amplification oligonucleotide of independent claim 442 (and dependent claims 443-457) requires a promoter sequence, the amplification oligonucleotide of independent claim 458 (and dependent claims 459-467, 472 and 473) and the amplification oligonucleotides of independent claim 474 (and dependent claims 475-484 and 489-491) cover amplification oligonucleotides having a promoter sequence. In this respect, the amplification oligonucleotide of claims 442-457 is not distinct from the amplification oligonucleotides of claims 458-467, 472-484 and 489-491, which the Examiner is required to demonstrate in support of a requirement for restriction. See MPEP § 806.05(c) at 800-42 (8th ed., August 2001).

Next, the Examiner alleges that the invention of claims 468-471 and 485-488 and the invention of claims 458-467, 472-484 and 489-491 are related as combination and subcombination. Here, the Examiner contends that the combination as claimed does not require the particulars of the subcombination as claimed *because the additional limitation of including a capture probe in the combination could confer patentability* so that the subcombination as claimed is not required for patentability. Applicants are confused by the Examiner's allegation since claims 468-471 depend, directly or indirectly, from claim 458, and claims 485-488 depend, either directly or indirectly, from

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claim 474. Furthermore, Applicants note that the Examiner has failed to demonstrate that those claimed kits which specifically include a capture probe "[do] not require the particulars of the subcombination as claimed for patentability," as required by MPEP § 806.05(c) at 800-42 (8th ed., August 2001). To the contrary, the particulars of the "subcombinations" set forth in independent claims 458 and 474 are necessarily included in dependent claims 468-471 and 485-488.

In addition to the arguments presented above, Applicants note that to support a requirement for restriction, the Examiner *must* also give reasons for insisting on restriction (*i.e.*, separate classification, status or field of search). *See* MPEP § 806.05(c) at 800-42 (8th ed., August 2001). Applicants submit that no such reasons have been provided by the Examiner.

For the reasons presented above, Applicants respectfully request the Examiner to reconsider the restriction requirement. If the Examiner's restriction requirement is maintained, then Applicants reserve their right to petition from the requirement under 37 C.F.R. § 1.144. Moreover, if the Examiner intends to maintain the restriction requirement, then Applicants respectfully submit that it will be necessary for the Examiner to provide them with a fully supported and complete two-way distinctness analysis, as required by MPEP § 806.05(c) at 800-42 (8th ed., August 2001).

Subject to Applicants' request for reconsideration, Applicants provisionally elect the invention of claims 458-467, 472-484 and 489-491.

Double Patenting Rejection

Claims 422-441 stand provisionally rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 444-465 of co-pending application Serial No. 09/565,427. Applicants submit that this rejection is inapposite since claims 422-441 were canceled in their Amendment dated September 19, 2001. Accordingly, withdrawal of this rejection is respectfully requested.

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Claims 458-467, 472-484 and 489-491 stand rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Van Gemen *et al.* (U.S. Patent No. 5,679,553). Applicants submit that this rejection was previously overcome for the reasons set forth in their Amendment dated September 19, 2001. Applicants further traverse this rejection for the reasons that follow.

The Examiner characterizes the invention of claims 458-467, 472-484 and 489-491 as being drawn to kits for amplifying a target nucleic acid sequence contained in a target nucleic acid which includes first and second amplification oligonucleotides, wherein:

... said first oligonucleotide contains a first base region which forms a stable hybrid with a second base region contained in said target nucleic acid under amplification conditions, wherein said second oligonucleotide contains a third base region which forms a stable hybrid with a fourth base region contained in said target nucleic acid, and wherein at least one of said first base region and said third base sequences contains one or more ribonucleotides modified to include a 2'-O-methyl substitution to the ribofuranosyl moiety; and that written instructions for use of said kits.

Applicants submit that the Examiner's characterization of Applicants' claimed invention is wrong. First, the kit of claim 458, and its dependents, comprise an *unlabeled* amplification oligonucleotide which includes a first base sequence containing one or more ribonucleotides modified to include a 2'-O-methyl substitution to the ribofuranosyl moiety, as well as *one or more reagents for performing an amplification reaction*. There is no requirement in these claims that a second amplification oligonucleotide be included. Second, the kit of claim 474, and its dependents, comprises first and second amplification oligonucleotides, but the first amplification oligonucleotide contains a first base sequence which hybridizes to a second base sequence *contained in said target nucleic acid 5' to said target sequence* under amplification conditions, and the second amplification oligonucleotide contains a third base sequence which hybridizes to a fourth base sequence *contained in a nucleic acid sequence complementary to at least a portion of said target nucleic acid 3' to said target*

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sequence under amplification conditions. Also, contrary to the Examiner's characterization of the claimed invention, neither independent claim requires the inclusion of "written instructions for use of said kits." Thus, the Examiner's stated reasons for this rejection are not based on Applicants' invention as claimed and, accordingly, this rejection is deemed to be an incomplete response to Applicant's Amendment dated September 19, 2001. *See* 37 C.F.R. § 1.104.

Notwithstanding, Applicants are submitting herewith a Declaration Under 37 C.F.R. § 1.131, executed by Michael M. Becker, Ph.D., Steven T. Brentano, Ph.D., and Mehrdad Majlessi, co-inventors of the subject application, which swears back of Van Gemen's U.S. priority date. This Declaration references and describes evidence demonstrating conception and reduction to practice by Dr. Brentano of 2'-O-methyl modified primers for use in amplifying target nucleic acid sequences prior to August 25, 1995 (all dates appearing in the original of Exhibit A have been redacted).

Exhibit A of the Declaration (Dr. Brentano's Laboratory Book No. 3222, pages 64-67) shows a study that was performed by Dr. Brentano prior to August 25, 1995 to test the efficacy of T7 primers containing 2'-O-methyl substitutions that he designed for use in a transcription-mediated amplification. *See* the Declaration at para. 2 and Exhibit A at p. 64. Each of these modified T7 primers was 50 bases in length and contained either 13 or 18 2'-O-methyl modified ribonucleotides at the 3' end, with the remaining bases being unmodified deoxyribonucleotides. To ensure that the modified T7 primers were capable of acceptably amplifying a target nucleic acid -- in this case an HIV target sequence -- Dr. Brentano further conducted tests with (i) identical, unmodified T7 primers, (ii) deoxyribonucleotide equivalent T7 primers, and (iii) samples containing no added target nucleic acid.

Dr. Brentano tested all of these primers under essentially identical amplification conditions and at varying concentrations of 8, 15 or 30 pmol. *See* the Declaration at para. 3 and Exhibit A at p. 65. Each sample included 30 pmol of unmodified non-T7 primer and either 5×10^5

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copies of an HIV target sequence or no added HIV target sequences. After sufficient time for a transcription-mediated amplification, a 1 μ l aliquot of each amplification reaction mixture was removed from each 100 μ l reaction mixture and added to 100 μ l of deionized water in order to dampen the amount of signal from these diluted samples. The results from each reaction mixture were determined using the Hybridization Protection Assay (HPA), (*see* specification at page 5, lines 10-18, for a description of HPA) employing a probe competition format and detecting the presence of acridinium ester label associated with probe hybridized to amplicon of the targeted HIV sequence. *See* the Declaration at para. 4 and Exhibit A at page 67.

As can be seen from the results presented on page 67 of Exhibit A, Dr. Brentano was able to demonstrate that the 2'-O-methyl modified primers used were capable of amplifying the targeted HIV sequence as efficiently as their unmodified and fully deoxyribonucleotide counterparts. The results presented in Exhibit A are broken down into groups of reaction mixtures as follows: (i) no target sequence ("-"); (ii) target sequence with no subsequent dilution of the amplification reaction mixture ("500 copies full format"); and (iii) target sequence with subsequent dilution of the amplification reaction mixture ("500 copies 1 μ l"). *See* the Declaration at para. 5. Each of these groups is then subdivided into reaction mixtures containing (i) no T7 primers ("N-8", "N-15" and "N-30"), (ii) T7 primers containing 13 3' end 2'-O-methyl modified ribonucleotides ("m13-8", "m13-15" and "m13-30"), (iii) T7 primers containing 18 3' end 2'-O-methyl modified ribonucleotides ("m18-8", "m18-15" and "m18-30"), (iv) unmodified T7 primers containing 13 3' end ribonucleotides, with the remaining bases being deoxyribonucleotides ("r13-8", "r13-15" and "r13-30"), and (v) unmodified T7 primers containing 18 3' end ribonucleotides, with the remaining bases being deoxyribonucleotides ("r18-8", "r18-15" and "r18-30"). For each designation, the second number indicates the amount of T7 primer in pmol added to the amplification reaction mixture. All results are presented in terms of relative light units (RLUs) detected.

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As a simple comparison of the results presented under these various groupings in Exhibit A clearly demonstrates, Dr. Brentano had conceived of and reduced to practice the use of primers containing 2'-O-methyl substituted ribofuronosyl moieties prior to the U.S. filing date of Van Gemen that were as effective in amplifying a target nucleic acid sequence as equivalent deoxyribonucleotide primers. Thus, Applicant submits that Van Gemen has been properly sworn back of by the Declaration and, accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

Applicants submit that the subject application is in condition for allowance and Notice to that effect is respectfully requested.

No fee is believed due in connection with this Reply. If Applicants are mistaken, please charge the amount due to Deposit Account 07-0835 in the name of Gen-Probe Incorporated.

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Certificate of Transmission

I hereby certify that this correspondence (and any referred to as attached) is being sent by facsimile to 703-872-9306 on the date indicated below to the Commissioner for Patents, Washington, D.C. 20231.

Respectfully submitted,

Date: February 6, 2001

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